REMARKS

Applicants would first like to thank Examiner Frank Lu for his time and helpful suggestions during the telephonic interview on February 12, 2010 with Applicants' representative, Cheryl H. Agris. The substance of the interview is provided below.

As discussed during the interview and as will be discussed in further detail below, claims 91, 101, 110, 113-116 and 119 have been amended to more distinctly claim the subject matter of the invention. Claim 92 has been canceled without prejudice. Applicants reserve the right to file continuation and/or divisional applications containing claims encompassing the canceled subject matter. The subject matter of canceled claim 92 has been incorporated into claims 91, 110 and 119. Thus, the amended claims contain no new matter and are supported by the specification.

Furthermore, claims 124-129 have been added to recite specific embodiments. Specifically, claims 124, 126 and 128 recite that the promoter is either a bacteriophage promoter or eukaryotic promoter; claims 125, 127 and 129 recite that the polymerase is either a bacteriophage or eukaryotic RNA polymerase. These new claims are supported by the specification on pages 36 (4-5 lines from the bottom), 38 (lines 12-13), 39 (3 lines from the bottom), 41 (lines 5-9) and Figure 4.

I. SUBSTANCE OF INTERVIEW

A. Brief Description of any Exhibit Shown or any Demonstration Conducted

Applicants submitted Figures 3 and 4 and pages 35-41.

B. Identification of Claims Discussed

Claims 91, 101, 110, 113-116 and 119 were discussed.

C. Identification of Specific Prior Art Discussed

As will be set forth in further detail below, Wagner et al. was discussed with respect to the rejections under 35 USC §112.

D. Identification of Principal Proposed Amendments of a Substantive Nature Discussed

Amendments to claims 91, 110 and 119 were discussed.

E. Identification of General Thrust of Principal Arguments presented to the examiner

An enabling disclosure of the claimed subject matter has been provided.

F. A General Indication of Any other Pertinent Matters Discussed

No other pertinent matters were discussed.

G. General Results or Outcome of the Interview

Applicants will present arguments showing that there is an enabling disclosure for the amended claims.

II. Objection to the claims

Claim 101 is objected to because of the following informality: "T7, T3, SP6" should be "T7 RNA polymerase, T3 RNA polymerase, SP6 RNA polymerase". Furthermore, Claim 113 or 114 or 115 or 116 is objected to because of the following informality: "said protein coding sense RNA" should be "said protein coded by said sense RNA".

In response, claims 101, 113-116 have been amended accordingly.

III. The Rejection Under 35 USC §112, First Paragraph (Enablement)

Claims 91-102, 104, 110-119, 122, and 123 have been rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for producing a specific nucleic acid comprising a sequence coding for a protein in a cell *in vitro* by introducing a conjugate formed by T7 RNA polymerase and a vector containing a promoter for T7 RNA polymerase and said nucleic acid comprising a sequence coding for a protein wherein the promoter for T7 RNA polymerase is upstream of said nucleic acid comprising a sequence coding for a protein (i.e., using said conjugate), does not

reasonably provide enablement for producing a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 in any kind of cell *in vivo* by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into the cell (i.e., using said conjugate recited in claims 91-102, 104, 110-119, 122, and 123)".

Two reasons are provided on page 10 and 11 of the Office Action:

> First, since the claims do not require that the RNA polymerase is bacteriophage T7 RNA polymerase which is a RNA polymerase capable of carrying out transcription with high promoter specificity and efficiency without involvement of any cellular transcription factor (see page 2114, right column from Chen *et at.*, Nucleic Acids Research, 22, 2114-2120, 1994) and do not limit sources of the cell and RNA polymerase, and it is known that other RNA polymerase such as RNA polymerase II can function only in the presence of cellular transcription factors (see Shilatifard *et at.*, Annu. Rev. Biochem.,72, 693-715, 2003 and attached definition for "RNA polymerase II" from Wikipedia, the free encyclopedia) and the mechanisms of RNA synthesis in prokaryotes and eukaryotes are totally different and prokaryotic transcription occurs in the cytoplasm while eukaryotic transcription is localized to the nucleus transcription" from Wikipedia, the free encyclopedia), it is unclear, if the RNA polymerase is not bacteriophage T7 RNA polymerase, how a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 can be produced in any kind of cell such as a prokaryotic cell by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into the cell when the RNA polymerase is an eukaryotic RNA polymerase in the absence of eukaryotic specific cellular transcription factors and how a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 can be produced in any kind of cell such as an eukaryotic cell by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into the cell when the RNA polymerase is a prokaryotic RNA polymerase in the absence of prokaryotic specific cellular transcription factors. Second, although claims are directed to the product itself not the method, the rejected claims require that the conjugated has abilities to be introduced into a cell *in vitro* and *in vivo*. Since the specification does not provide a guidance to introduce a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into a cell *in vivo* such as a cell in human body and there are a number of differences between *in vitro* models and the *in vivo* situation (see White et al., Pharmacotherapy, 21,

> 292S-301S, 2001), it is unclear how a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 can be introduced into a cell *in vivo* such as a cell in human body so that a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 can be produced in human body.

Applicants respectfully traverse the rejection. First, before responding to the rejection, Applicants wish to point out that claims 91, 110 and 119 have been amended to recite that the conjugate has the recited characteristics when introduced into a **eukaryotic cell**, that the RNA polymerase is **cognate to said promoter (i)** and that the segment of the specific nucleic acid produced by the conjugate **is produced by transcription from the promoter (i) by the polymerase (iii).** These amendments have been introduced to advance prosecution. In particular, these claims now more specifically point out the relationship between the nucleic acid product and the promoter and its polarity by adding the limitation "wherein said segment (ii) is produced by transcription from said promoter (i) by said polymerase (iii)". In Applicants view and for reasons discussed below, these amended claims and dependent claims 93-102, 104, 111-118 and 122-123 are enabled by the specification.

First, Applicants assert that the claims are enabled for more than a T7 polymerase. Applicants note that examples of various bacteriophage and eukaryotic polymerases are provided in the specification. These include the bacteriophage polymerases SP6 and T3 polymerases and the eukaryotic polymerases RNA polymerase III (see page 41). Further, various examples of both eukaryotic and bacteriophage promoters are provided as well and include: Pol I, Pol II, Pol III, SV40 and T7 (see pages 38 and 41).

It has been questioned in the Office Action and during the interview with the examiner whether there is evidence as to whether any other polymerase besides T7 can function independently of cellular transcription factors. The Office Action refers to Wagner et al., US Patent No. 5,591,601 to support his assertion. However, Applicants note that Wagner states on column 8, lines 5-12:

> Most preferable is a RNA polymerase that is a small single unit enzyme that does not require host cell factors for activity, that recognizes its cognate promoter sequence with a high degree of specificity, and that is highly active. Examples of RNA polymerases suitable for use in the

> present invention include, but are not limited to, the RNA polymerases of the T7, T3, SP6 or K11 bacteriophages or of the RNA polymerases of mitochondria.

Various phage RNA polymerases are treated in an equivalent manner in US Patent No. 5,550,035 (attached hereto as Exhibit 1 and listed in the Supplemental Information Disclosure Statement), where it is stated in col. 4, lines 12-35:

> The RNA polymerase genes which may be used in accordance with the present invention include any RNA polymerase that will function in the cytoplasm of a eukaryotic cell in the presence of a DNA-based cytoplasm virus. For purposes of example, particularly suitable are RNA polymerase genes from bacteriophage, bacterial viruses, and especially the T7, SP6, GH1, and T3 viruses. For purposes of illustrating a preferred embodiment of the present invention, and not limitation, the T7 RNA polymerase gene will be discussed in detail. The T7 RNA polymerase gene is isolated from the prokaryotic (viral) T7 bacteriophage. The T7 bacteriophage infects bacteria, but not eukaryotic cells. The T7 RNA polymerase is highly specific for promoter sequences contained within the bacteriophage genome. Accordingly, it is understood that the chances of finding a similar sequence in eukaryotic or other DNA are very nominal. For a further discussion on the specificity and individual promoters recognized by the bacteriophage RNA polymerases see Chamberlin et al, The Enzymes, vol. 15, pp. 82-108 (1982); and Dunn et al, J. Mol. Biol. 166, pp. 477-535 (1983). It is understood that the discussion with respect to the T7 RNA polymerase generally applies to other RNA polymerases, especially the bacteriophage RNA polymerases mentioned above.

Applicants also note that Jorgensen et al., 1991, "Specific Contacts between the Bacteriophage T3, T7 and SP6 RNA Polymerases and their Promoters", J. Biol. Chem. 266:645-651 (attached hereto as Exhibit 2 and submitted with the Supplemental Information Disclosure Statement) stated in the second sentence that T7, T3 and SP6 RNA polymerases are able to function in the absence of any additional protein factors. Clearly, there are certainly other RNA polymerases besides T7 RNA polymerase that can function independently of cellular transcription factors and these RNA polymerases were clearly well known in the art as of the priority date of the instant application.

Applicants wish to further point out that once in the cell, the elements that are responsible for production of a specific nucleic acid should all be present. The art is replete with examples of nucleic acid constructs that are introduced into cells and make use of native polymerases, such that it is considered to be standard methodology (see, for example, Lopata et al., 1986, Proc. Natl. Acad. Sci. 83: 6677-6681 and Pine, 1992, J. Virol. 66:4470-4478, attached hereto as Exhibits 3 and 4 respectively and also submitted with the Supplemental Information Disclosure Statement). In addition, the special case where an RNA polymerase is added to a cell (either as the protein itself or as a co-transfected nucleic acid construct that codes for it) has also been shown in the literature to be completely functional in terms of generating a nucleic acid product by transcription of its cognate promoter. As long as an RNA polymerase and a nucleic acid that has the appropriate promoter are both present in a cell, there would be no expectations of any particular difficulty in expression from that promoter.

It is further noted in the Office Action that the mechanisms of RNA synthesis in prokaryotes and eukaryotes are totally different and prokaryotic transcription occurs in the cytoplasm while eukaryotic transcription is localized to the nucleus transcription. In response, Applicants note that prior art has shown that transient transfections of plasmid DNA that utilize eukaryotic polymerases native to the transfected cell can transcribe plasmids that are present in the cytoplasm (see, for example, Cochran et al., 1985, Proc. Natl. Acad. Sci. USA 82:19-23, attached hereto as Exhibit 5 and submitted with the Supplemental Information Disclosure Statement). In an effort to advance prosecution, Applicants have also added a further limitation to the claims that the target cell is a eukaryotic cell as follows "which when introduced into a **eukaryotic** cell". Applicants also note that a transient transfection system was disclosed by Moss et al. in US Patent No. 5,550,035 which utilized phage polymerase in the presence of a DNA-based cytoplasmic virus to facilitate expression of a foreign gen in the cytoplasm of a eukaryotic cell. Thus, the cell would provide an environment that will be appropriate for transcription by either a phage polymerase or by a eukaryotic polymerase.

Finally, Applicants note that concerns were raised with respect to the utility of the claimed construct in vivo. In response, Applicants assert that a lack of specific guidance in the specification for *in vivo* delivery of a protein-nucleic acid conjugate is not

relevant to the pending claims that are descriptions of compositions, not methods. The language "when introduced into a cell", involves a description of the properties of the composition when it is in a cell and not a description of the history of how it was introduced. Thus, the division between *in vivo* and *in vitro* is not part of the claim and is only an artificial demarcation based on potential methods of introduction. Furthermore, as noted in the previous substantive response, there have been descriptions of situations where protein-nucleic acid complexes have been introduced into cells by *in vivo* means (Gao et al., 1993 and Wu et al., 1988, cited in the previous response). Again, we believe that methods that are appropriate for *in vivo* delivery protein-nucleic acid complexes are also appropriate for delivery of protein-nucleic acid conjugates. In terms of predictability, Applicants assert that the above cited literature should be adequate for this purpose with the only caveat being that the particular efficiency of this delivery may be of a variable nature.

In view of the above arguments, Applicants assert that the rejections under 35 USC §112, first paragraph have been overcome. Therefore, Applicants respectfully request that the rejection under 35 USC §112, first paragraph be withdrawn.

IV. The Rejections Under 35 USC §112, Second Paragraph

Claims 101 and 104 have been rejected under 35 U.S.C. 112, second paragraph. The Office Action specifically states:

> Claim 101 is rejected as vague and indefinite. Since claim 91 only has one RNA polymerase, it is unclear why said RNA polymerase recited in the claim can comprise a combination of T7 RNA polymerase, T3 RNA polymerase, and SP6 RNA polymerase. Please clarify.
>
> Claim 104 recites the limitation in "claim 103" of the claim. There is insufficient antecedent basis for this limitation in the claim because claim 103 has been deleted. Please clarify.

Applicants respectfully traverse the rejection. However, in order to advance prosecution, claim 101 has been amended to recite that the RNA polymerase comprises T3, T7 or SP6. Furthermore, claim 104 has been amended to recite that it depends from claim 91.

In view of the amendment of claims 101 and 104, the rejections under 35 USC §112, second paragraph have been overcome. Therefore, Applicants respectfully request that the rejections under 35 USC §112, second paragraph be withdrawn.

SUMMARY AND CONCLUSIONS

It is Applicants belief that the pending claims are in condition for allowance. However, if a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

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